II. DISCUSSION OF THE AMENDMENTS

Claims 32-38 are pending in the application. Claim 32 has been amended by the present amendment.

Claim 32 has been amended to more clearly point out that the presently claimed covalently linked sensing moiety is an exogenous sensing moiety. Support for this amendment is found in the specification on p. 3, ll. 10-18:

> The "covalent attachment" of one or more sensing moieties to pore-forming or pore-subunit polypeptides to create the "modified, pore-forming, sensing pore-subunit polypeptides" of the present invention means that at least a first "*exogenous*" sensing moiety is covalently attached to the polypeptide. This differs from pore-subunit polypeptides in which the only modification(s) is one or more mutations within the amino acid sequence of the polypeptide itself. Although the sensing moiety is engineered into such polypeptides, in contrast to the native polypeptide sequence, such engineered, modified or "mutant" polypeptides still comprise an "endogenous" sensing moiety.

Claim 32 has been amended to more clearly point out that the covalently linked exogenous sensing moiety of the present invention preferentially binds a specific analyte, compared to other 'similar' agents that may be in the sample. This amendment is supported by the specification at page p. 54, ll. 26-29, "This study shows that the DNA-nanopore was able to discriminate, on the single molecule level, between two 30 nt-long ssDNA strands differing only by a single base."

III. RESPONSE TO THE OFFICE ACTION

A. The Church reference

Claims 32-38 have been rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Pat. No. 5,795,782, by Church et al. (the Church reference). The Church reference is generally directed to methods of characterizing linear polymer molecules by measuring physical changes across an interface between two pools of media as the linear polymer traverses the interface and

monomers of the polymer interact with the interface. The Church reference proposes several structures for facilitating such measurements. None of the structures proposed by the Church reference teach every element of the instant claims. The Church reference therefore does not anticipate the instant claims.

In formulating his rejection under 35 U.S.C. § 102(b), the Examiner has combined elements from the several embodiments proposed in the Church reference, but has failed to point to a single embodiment that anticipates the present claims. This is not proper grounds for a 102 rejection. Assuming, *arguendo*, that the Church reference teaches all of the elements of the present claims, the Church reference still does not anticipate the present claims unless each of the elements are present in the <u>same disclosed invention</u>. The Examiner is not free to pick and choose one element from one embodiment, another element from another embodiment, and so on, to reconstruct the present claims. See, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) ("Every element of the claimed invention must be literally present, <u>arranged as in the claim</u>. [ ] The <u>identical invention</u> must be shown in as complete detail as is contained in the patent claim.").

The Examiner cites to col. 3, ll. 38-55 of the Church reference as anticipating the element of covalent linkage. These lines are reproduced below:

> The protein channels or pores of the invention can include those translated from one or more natural and/or recombinant DNA molecule(s) which includes a first DNA which encodes a channel or pore forming protein and a second DNA which encodes a *monomer-interacting portion of a monomer polymerizing agent* (e.g., a nucleic acid polymerase). The expressed protein or proteins are capable of non-covalent association or *covalent linkage* (any linkage herein referred to as forming an "assemblage" of "heterologous units"), and when so associated or linked, the polymerizing portion of the protein structure is able to polymerize monomers from a template polymer, close enough to the channel forming portion of the protein structure to measurably affect ion conductance across the channel. Alternatively, assemblages can be formed from unlike

> molecules, e.g., a chemical pore linked to a protein polymerase, but these assemblages still fall under the definition of a "heterologous" assemblage.

The above described embodiment does not anticipate the present claims even if the *monomer-interacting portion of a monomer polymerizing agent* (e.g., a nucleic acid polymerase) is considered to be a sensing moiety covalently linked to the pore because such a polymerizing agent does not <u>preferentially bind a specific analyte</u>. If a sample containing two different DNA polymers having different sequences were measured using this sensor, there is no indication in the Church reference that this sensor would preferentially polymerize monomers from one template DNA, compared to the other. Contrarily, one would assume that the monomer polymerizing agent would polymerize monomers from *any* template polymer. This embodiment is not identical to the claimed invention because it lacks the claim element "preferentially binding with a specific analyte."

The Examiner cites to a different embodiment at col. 3, ll. 28-36 as teaching a sensing moiety capable of binding with the analyte. These lines are reproduced below:

> Another preferred type of passage is a protein which includes a portion of a *bacteriophage receptor* which is capable of binding all or part of a bacteriophage ligand (either a natural or functional ligand) and transporting bacteriophage DNA from one side of the interface to the other. The polymer to be characterized includes a portion which acts as a specific ligand for the bacteriophage receptor, so that it may be injected across the barrier/interface from one pool to the other.

Assuming that the bacteriophage receptor is what the Examiner considers as the sensing moiety, the Church reference does not indicate that this receptor is *covalently linked* to the pore-subunit polypeptide or that it is an *exogenous* sensing moiety. In fact, the Church reference (col. 13, ll. 55-66) teaches that a bacteriophage receptor is itself a pore:

> The LamB pore Maltoporin (LamB) is an outer membrane protein from E. coli that *functions as a passive diffusion pore* (porin) for small molecules and as a specific transport pore for passage of maltose and maltodextrins.

> *It is also the receptor for bacteriophage lambda.* Three identical copies of the LamB gene product assemble to form the native pore. *Each subunit (MW .about.48,000) is composed of predominantly beta-structure and is a pore in itself, though it is thought that the three pores fuse into one at the periplasmic side of the membrane.*

The bacteriophage receptor is itself a pore assembly comprising three pore-subunit polypeptides sufficient to form a pore. However, there is no indication in the Church reference that any of these pore subunits are a *modified pore-subunit polypeptide comprising a pore-subunit polypeptide covalently linked to an exogenous sensing moiety.* It does not make sense to modify the pore subunits by adding a covalently linked exogenous sensing moiety because the Church reference teaches the polymer to be characterized includes a portion that acts as a specific ligand for the *unmodified* LamB pore. Therefore, no covalently linked exogenous sensing moiety is needed.

Because the Examiner has failed to cite an embodiment in the Church reference that contains very element of the claimed invention wherein the elements are arranged as in the present claims, Applicants respectfully request that the rejection under 35 U.S.C. § 102 over the Church reference be withdrawn.

2. The Braha reference

Claims 32-33, 35 and 38 were rejected under 35 U.S.C. 102(e) as being anticipated by Braha et al., *Chemistry & Biology*, 4(7): 497-505, 1997 (the Braha reference). Specifically, the Examiner alleges that the Braha reference anticipates the instant claims because it discloses a method of detecting divalent metal ions using a bacterial pore-forming protein having receptor sites. Applicants respectfully traverse.

The Braha reference is directed to a biosensing architecture utilizing an α-hemolysin, in which pore-subunits have been engineered to contain a binding cite for a divalent metal ion. *See*,

Braha reference, abstract and Figure 1. The only modifications to the pore-subunit polypeptides disclosed in the Braha reference that are relevant to the sensing mechanism are mutations within the amino acid sequence of the polypeptide itself, i.e., the peptides comprise only an "endogenous" sensing moiety.

In contrast, the instant claims are directed to a method of detecting an analyte using a pore assembly wherein at least one of the pore-subunit polypeptides is modified to contain an "exogenous" sensing moiety. In the present Office Action, the Examiner stated that "exogenous" attachment is not recited in the claims. This element has been added to the claims by the present amendment. Applicants therefore respectfully request that the rejection over the Braha reference be withdrawn.

* * *

The Examiner is invited to contact the undersigned patent agent at 713-787-1558 with any comments relating to the referenced patent application.

Respectfully submitted,

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